Treatment Protocol for COVID-19 (SARS-CoV-2) for RWJ University Hospital, New Brunswick (April 9, 2020 10pm)

Use of experimental drugs via clinical trials or compassionate use are rapidly evolving. **New drafts will be published as more information becomes available – always note date/time of version**. For protocol updates, contact: Nav Narayanan, PharmD, MPH (navan12@pharmacy.rutgers.edu)

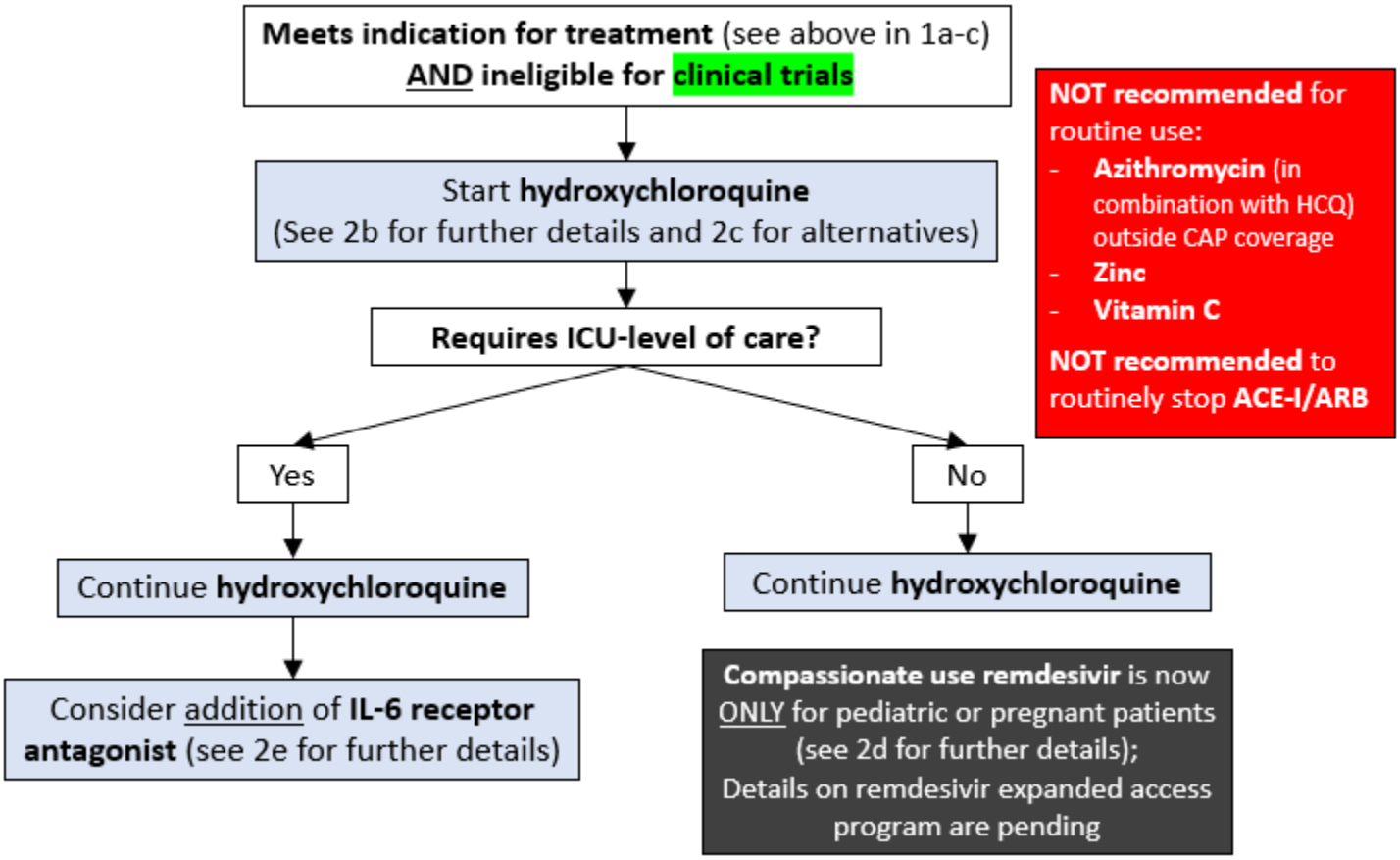
READ THIS FIRST

RWJ NB is a study site for multiple clinical trials – **PRIMARY therapeutic option is enrollment in a clinical trial.** If ineligible for an RCT listed here, proceed with default clinical care protocol below. See INCLUSION and EXCLUSION criteria for each RCT in **Appendix A and B.** For enrollment evaluation **CONTACT:**

- **Remdesivir RCTs**: Pinki Bhatt, MD (pb518@rwjms.rutgers.edu) and Fei Chen, RN (chenf2@rwjms.rutgers.edu)
- **Rutgers RCT (CINJ 002011) HCQ alone vs. HCQ plus azithromycin**: on Mon-Fri, 730a-530p, call: 732-235-7356 or email: statewide_research@cinj.rutgers.edu

In an inpatient with **positive SARS-CoV-2 PCR test** or **highly suspected person under investigation** for COVID-19 (contact with a confirmed case or high-risk travel history or consistent clinical presentation), we recommend the following:

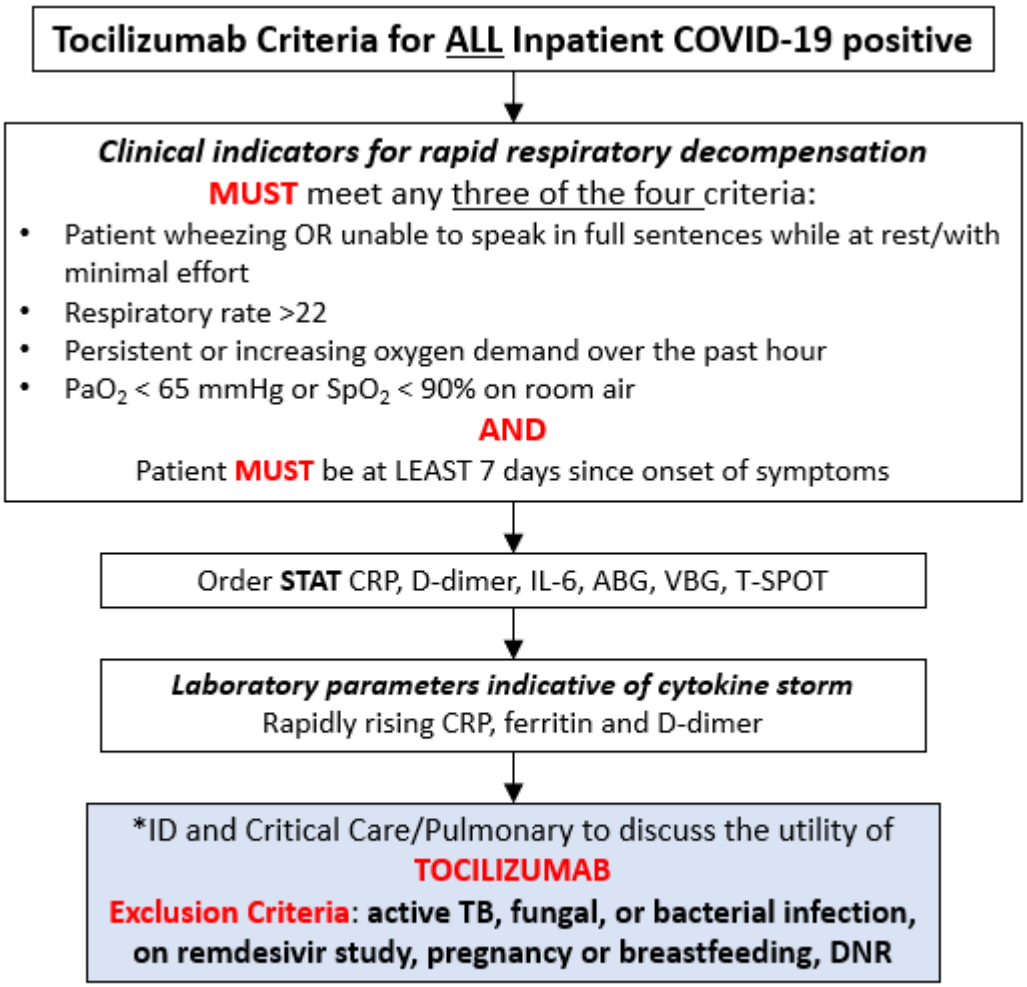
1. Treatment Indications – consider treatment for any **ONE** of the following groups:
    a. Requiring ICU-level of care
    b. Requiring any supplemental oxygen (if not on oxygen at baseline)
    c. Lower respiratory tract disease with risk factors for progression to severe disease:
        i. Older age (> 60 years)
        ii. Immunocompromised
        iii. Significant chronic comorbidities (including but not limited to diabetes, pulmonary disease [e.g. COPD], cirrhosis, CKD, cardiovascular disease, hypertension, and any other medical conditions based on clinical judgement by ID attending physician)



2. Treatment recommendations for qualifying groups per treatment indications as above:
    a. **ID approval** to initiate any COVID-19-specific treatment (supportive care as usual by primary team):
        i. HCQ is NOT restricted (i.e. does not require ID consult or ID approval)
            1. In general, aim to stay with 5-day regimen as listed below unless severely/critically ill
            2. Consider discontinuation if SARS-CoV-2 PCR is negative and low suspicion for COVID-19
        ii. Tocilizumab requires ID approval via ID attending MD covering ID ICU COVID-19 patients

b. Treat with **hydroxychloroquine (HCQ)**
    i. Use as primary treatment if not a candidate for remdesivir compassionate use (see 2d below) or in the interim pending receipt of remdesivir for compassionate use
    ii. HCQ dose: 400 mg BID x 1 day, then 400 mg ONCE DAILY for 4 more days = 5-day regimen (may consider extending duration) – see rationale below for expected drug exposure
        1. Will now do ONCE DAILY maintenance as standard dosing (over the previous BID dosing) to limit entry into patient room thereby limiting additional exposure
        2. All patients on the ventilator should receiving HCQ suspension – see compounding instructions below at section 2f; order built in EHR (order item: hydroxychloroquine suspension 25 mg/mL)
        3. No dose adjustment needed in renal impairment
        4. Most toxicity associated with long-term use but for short-term use, still consider:
            a. QTc prolongation – mainly if on other concomitant QTc prolonging medications
            b. It is NOT recommended to routinely check for G6PD deficiency in all patients
c. Alternative antiviral treatment options: **chloroquine** 500 mg PO BID for 10 days
d. **Remdesivir** via **compassionate use** through Gilead (apply via: http://rdvcu.gilead.com/)
    i. **ONLY for PREGNANT women or PEDIATRIC patients – pending expanded access program**
    ii. Inclusion: hospitalization | confirmed SARS-CoV-2 by PCR | invasive mechanical ventilation
    iii. Exclusion: multiorgan failure | requiring pressors | ALT >5x ULN | CrCl <30 or any dialysis
    iv. May need to **discontinue** hydroxychloroquine (or alternative) prior to start of remdesivir (follow Gilead's compassionate use protocol for remdesivir for definitive instructions)
e. In addition to antiviral treatment, for patients requiring ICU-level of care for COVID-19-related severe pulmonary complications (e.g. ARDS or continued deterioration on mechanical ventilation or before need for intubation) – consider **adjunctive use of IL-6 receptor antagonist**, in consult with ICU team
    i. See **FLOW CHART** below for clinical criteria for use of tocilizumab
    ii. **Tocilizumab** (Actemra)
        1. Dose: <30 kg: 12 mg/kg | ≥30 kg: 8 mg/kg | **maximum dose**: 800 mg per dose IV
            a. 50-69 kg → give **400 mg** IV
            b. 70-85 kg → give **600 mg** IV
            c. >85 kg → give **800 mg** IV
        2. If clinical improvement does not occur after the first dose, up to **ONE** additional dose may be administered (with at least an 8 hour interval between consecutive doses)
            a. Number of additional doses is highly dependent on current drug supply
        3. Send IL-6 plasma level (https://www.mayocliniclabs.com/test-catalog/Overview/63020)
            a. Send out test, won't likely influence real-time decision-making but potentially useful for further understanding of pathogenesis of severe COVID-19
        4. Warning related to tuberculosis reactivation – send T-SPOT test to assess for LTBI
            a. Do not hold therapy pending results – can treat LTBI later as needed
f. **Extemporaneous compounding for HCQ** (25 mg HCQ/mL) for pharmacy to make and dispense
    i. Crush fifteen 200 mg tablets in mortar to fine powder
    ii. Add 15 mL of Ora-Plus, mix to uniform paste
    iii. Mix while adding additional 45 mL of vehicle
    iv. Mix while adding sterile water (SW) for irrigation to almost 120 mL
    v. Transfer to bottle, rinse mortar with SW and QS to make 120 mL
    vi. Stable up to 30 days stored in the dark at room temperature or refrigerated
    vii. References: Allen, et al. AJHP 1998;55:1915-20. Pesko LJ, Am Druggist 1993;207-57.
g. **COVID-19 drug interactions** (University of Liverpool – reliable resource for HIV and HCV drugs)
    i. http://www.covid19-druginteractions.org/

Tocilizumab Clinical Criteria for Use FLOW CHART



**To prevent delay in administration of tocilizumab please contact covering ID attending as soon as a patient is identified that meets above criteria*

Rationale and Commentary for Therapeutic Options

- **Hydroxychloroquine (HCQ)** – has the same mechanism as chloroquine and more tolerable safety profile
    - HCQ was found to be more potent than chloroquine in vitro [Yao X et al]
    - Based on PBPK models, predicts lung tissue concentrations, the optimal dosing for SARS-CoV-2 is 400 mg BID (loading dose) for 1 day then 200 mg BID for 4 more days → 3x time the potency of chloroquine 500 mg BID for 5 days [Yao X et al]
    - Multiple dosing regimens are proposed including use of 400 mg once daily as the maintenance dosing [Yao X et al]
    - Both HCQ and chloroquine decrease viral replication in a dose-dependent manner [Yao X et al]
    - Despite a 5 day treatment regimen, drug concentrations in the lungs were still above the target on day 10
    - Both HCQ and chloroquine have immunomodulatory effects [Yao X et al] → HCQ is a potential ideal drug as it can inhibit virus via antiviral effects and mediate the cytokine storm via immunomodulatory effects
    - There is a small ongoing clinical trial in China for HCQ in COVID-19
    - A small RCT (n=62) from China was recently published preprint (not peer-reviewed) – HCQ 400 mg daily for 5 days (and supportive care) vs. supportive care alone. Severe and critical cases of COVID-19 were excluded. The primary outcome, time to clinical recovery (normal temp and cough cessation >72 hrs), was ~1 day faster in patients receiving HCQ. Numerically, in patients receiving HCQ, there was also improvements in chest imaging and less patients who progressed to severe illness. Small RCT showing moderate benefit in patients with mild-moderate COVID-19. [Chen Z et al]

- **Azithromycin** – in a small French study, the combination of hydroxychloroquine plus azithromycin (n=6) had a higher rate of "virologic cure" vs. hydroxychloroquine alone vs. control [Gautret P et al]. Rationale for NOT recommending for routine use against COVID-19 (maybe used as part of empiric CAP coverage if needed).
    - Study is essentially a case series ("control" group is selected from different hospital)
    - The "azithromycin plus HCQ" group has inherent selection bias and is likely confounded - the signal of potential benefit may simply be driven by differences in the patients (e.g. differences in baseline viral load – not a balanced distribution between groups).
    - There are no prior in vitro or in vivo data to corroborate the activity or clinical utility of azithromycin specifically for SARS-CoV-2
    - With limited to likely no benefit with azithromycin to be concluded from the French study, there is only risk of significant cardiac complications (QTc prolongation). This is particularly concerning given that cardiac comorbidities are a risk factor for severe COVID-19 – main principle is to do no harm in light of no valid observable clinical benefit
    - Additionally, there are no clinical outcomes in the French study, so we don't know if the faint (likely confounded) signal of viral reduction benefit actually equates to clinical benefit. Many patients were asymptomatic or only had URI in the first place
    - The follow up French study provides no significant value for clinical application – all patients (n=80) were treated with HCQ plus azithromycin BUT there was no comparator group so unable to assess the benefit of addition of azithromycin. Additionally, the patient population was much less severe – approximately half the patients were either asymptomatic or had upper respiratory infection and only 15% required oxygen therapy. [Gautret P et al]

- **Chloroquine** – based on news briefing from China, there is indication that chloroquine has demonstrated marked efficacy and acceptable safety in treating COVID-19 associated pneumonia in multicenter clinical trials conducted in China [Gao et al]. Full results yet to be published.
    - Thus far, results from > 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in 1) inhibiting the exacerbation of pneumonia, 2) improving lung imaging findings, 3) promoting a virus-negative conversion, and 4) shortening the disease course [Gao et al]
    - Chloroquine is recommended for inclusion in the next version of the Guidelines for the Prevention, Diagnosis, and Treatment of Pneumonia Caused by COVID-19 issued by the National Health Commission of the People's Republic of China. [Gao et al]
    - In the early in vitro studies, chloroquine was found to block COVID-19 infection at low-micromolar concentration, with a half-maximal effective concentration (EC50) of 1.13 μM and a half-cytotoxic concentration (CC50) greater than 100 μM [Wang et al]

- **Remdesivir** – experimental antiviral drug in phase 3 clinical trials for COVID-19 as well as available for compassionate use for COVID-19
    - Broad-spectrum antiviral with in vitro activity against (not full list) Ebola virus, Marburg virus, Nipah virus, Hendra virus, RSV, and human and zoonotic coronaviruses [Ko et al, Martinez]

- Although when tested for Ebola, outcomes were not favorable, the clinical safety profile in humans appear reasonable [Ko et al]
- Remdesivir appears to have a high genetic barrier for viral resistance with decreased fitness and pathogenicity in the remdesivir-resistant mutants [Ko et al, Martinez]

- **Tocilizumab** – IL-6 receptor antagonist currently used for treatment of cytokine release syndrome in CAR T-cell therapy patients at RWJ-NB. It has been used in China in a case series of 21 patients with positive outcomes – most patients were severely ill (based on respiratory function measures) but not mechanically ventilated [Xu X et al]. It has been used in other countries (e.g. Italy) and recommended in the Chinese national treatment guidelines. This is currently in phase 3 clinical trial in China [ChiCTR2000029765].
  - Dysregulation of immune response, especially T lymphocytes, might be highly involved in the pathological process of COVID-19 [Qin C et al]
  - Severe cases tend to have lower lymphocytes counts, higher leukocytes counts and neutrophil-lymphocyte-ratio (NLR), as well as lower % of monocytes, eosinophils, and basophils. Most of severe cases demonstrated elevated levels of infection-related biomarkers and inflammatory cytokines. The number of T cells decreased, and more hampered in severe cases [Qin C et al]
  - Most patients in [Qin C et al] to have lymphopenia, higher infection-related biomarkers (i.e. procalcitonin, erythrocyte sedimentation rate, serum ferritin, and C-reactive protein) and several elevated inflammatory cytokines (i.e. tumor necrosis factor (TNF)- α , interleukin (IL)-2R and IL-6), and there were numerous differences in blood cell counts and infection related biomarkers between severe group and non-severe group [Qin C et al]
  - Inflammatory cytokines were also elevated in severe cases than the non-severe ones, including interleukin (IL)-2R, IL-6 (25.2 vs 13.3 pg/mL; $P < 0.001$), IL-8, IL-10, and TNF-α. [Qin C et al]
  - Although there is no direct evidence for the involvement of pro-inflammatory cytokines and chemokines in lung pathology during COVID-19, the change of laboratory parameters, including elevated serum cytokine, chemokine levels, and increased NLR in infected patients were correlated with the severity of the disease and adverse outcome, suggesting a possible role for hyper-inflammatory responses in COVID-19 pathogenesis. [Qin C et al]
  - Novel information about dysregulated immune response in COVID-19 patients: SARS-CoV-2 might mainly act on lymphocytes, especially T lymphocytes, induce a cytokine storm in the body, and generate a series of immune responses to damage the corresponding organs. [Qin C et al]
  - Non-survivors were observed to have significantly higher IL-6 levels versus survivors consistent with the pathophysiology of severe COVID-19 (i.e. cytokine storm and immune dysregulation) [Young et al]

- **Lopinavir/ritonavir** – why not a "preferred" option in this protocol?
  - The current data and evidence for any recommendation in this protocol is limited to none – there is no "preferred" options given the novelty of this virus and disease (i.e. no proven therapeutics exist)
  - Some data indicate in vitro and in vivo activity against SARS-CoV and MERS-CoV but it is questionable if this translates to activity and effectiveness versus SARS-CoV-2 [Martinez]
  - Clinical benefit was equivocal and "decline in viral load as indicated by the cycle threshold value from NP swabs also appeared similar between those treated and not treated with lopinavir-ritonavir." [Young et al]
  - In the Lancet study from Wuhan examining predictors of mortality, "we did not observe shortening of viral shedding duration after lopinavir/ritonavir treatment in the current study." [Zhou et al]
  - This is consistent with anecdotal communication from IDSA IDea Exchange where Doug Richman stated in vitro susceptibility of COVID-19 is >100 fold less than is wild type HIV to lopinavir and PI-resistant mutants of HIV are even more susceptible than COVID-19 – essentially noting the relatively poor potency of lopinavir against COVID-19. Additionally, activity against MERS-CoV is debatable [Martinez].
  - KEY UPDATE: RCT from China published in NEJM March 18, 2020 evaluated LPV/r (plus SOC) vs. SOC only (oxygen, ventilation, antibiotics, pressors, RRT, ECMO) in hospitalized adults with severe COVID-19 (an oxygen saturation (Sao2) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (Pao2) to the fraction of inspired oxygen (Fio2) of less than 300 mm Hg). There was NO DIFFERENCE in the primary endpoint, time to clinical improvement or secondary endpoints, mortality at 28 days and detectable viral RNA at various time points. In hospitalized adult patients with severe Covid-19, no benefit was observed with lopinavir−ritonavir treatment beyond standard care. There are limitations to this study but there is no other compelling data to advocate for routine use to treat Covid-19 patients.

- **Ribavirin** – data conflicting on patients with MERS-CoV infections that were treated with a combination of ribavirin and IFN (either α2a or β1). Significant toxicity – limits potential as antiviral agent [Martinez].
  - Known data is use in combination with interferon with mixed results at best for MERS-CoV infections – the combination, even if desirable, is relatively toxic and therefore unfavorable

- **Corticosteroids** – have no effect on mortality and may result in delayed viral clearance [Huang et al]. NOT recommended by CDC specifically for COVID-19 management up front, unless indicated for other evidence-based reasons (e.g. COPD exacerbation or septic shock) per those guidelines [CDC].

- **ACE inhibitors/ARBs** – there is a working HYPOTHESIS (no clinical or experimental data at this time) that patients on these drugs maybe at increased risk for developing severe disease [Fang et al]
    - SARS-CoV-2 binds to ACE2, expressed by epithelial cells of lung, intestine, kidney and blood vessels
    - Expression of ACE2 is increased/upregulated in patients with DM and hypertension, who are treated with ACE inhibitors or ARBs. ACE2 is also increased by TZDs and ibuprofen.
    - Increased expression of ACE2, in theory, would facilitate infection with COVID-19
    - In theory, patients with cardiac diseases, hypertension, or diabetes, who are treated with ACE2-increasing drugs, are at higher risk for severe COVID-19 infection – no evidence CCBs increase ACE2 expression so [Fang et al] raise CCBs can be potential alternative. This is not validated by any data.
    - The Council on Hypertension of the European Society of Cardiology strongly recommend that physicians and patients should continue treatment with their usual anti-hypertensive therapy because there is no clinical or scientific evidence to suggest that treatment with ACEi or ARBs should be discontinued because of the Covid-19 infection. [de Simone]
    - HFSA/ACC/AHA Statement Addresses Concerns Re: Using RAAS Antagonists in COVID-19: "The continued highest standard of care for cardiovascular disease patients diagnosed with COVID-19 is top priority, but there are no experimental or clinical data demonstrating beneficial or adverse outcomes among COVID-19 patients using ACE-I or ARB medications. We urge urgent, additional research that can guide us to optimal care for the millions of people worldwide with cardiovascular disease and who may contract COVID-19. These recommendations will be adjusted as needed to correspond with the latest research."
    - NEJM Special Report – Vaduganathan M, et al. conclusion = RAAS inhibitors should be continued in patients in otherwise stable condition who are at risk for, are being evaluated for, or have Covid-19.

- **NSAIDs** – there is a theoretical concern that ACE2 upregulation by NSAIDs may lead to worse outcomes [Fang et al]. The WHO clarified on 3/20/2020 that it does NOT recommend avoiding NSAIDs. There is no evidence to support potential worse outcomes as well as no evidence to prove NSAIDs are safe in COVID-19 patients. Consider use of acetaminophen instead of NSAIDs for any acute therapeutic needs in COVID-19 patients but avoid discontinuing necessary NSAID therapy outside of COVID-19 (e.g. low-dose aspirin). Also, in general NSAIDs should be avoided in patients with pre-existing renal dysfunction or in sepsis (to avoid renal injury).

- **Vitamin C** – there is no published data to support use – this is NOT recommended for routine use in COVID-19 patients for treatment. There is an ongoing clinical trial in China studying the benefit of vitamin C infusion for the treatment of severe COVID-19. https://clinicaltrials.gov/ct2/show/NCT04264533. Results could inform future potential use but there is no preliminary data to guide any type of use or regimen. Use for other indications, such as sepsis and ARDS, an infusion of vitamin C compared with placebo did not significantly improve organ dysfunction scores or alter markers of inflammation and vascular injury [Fowler et al]. Also, no data for use in other coronaviruses (SARS, MERS).

- **Zinc** – there is no published data to support use – this is NOT recommended for routine use in treatment of COVID-19.

- **Ivermectin** – this drug is NOT recommended for use to treat COVID-19. There is one study by Caly et al that observed significant viral RNA reduction when using ivermectin against SARS-CoV-2 in an in vitro cell model. Using rough calculations (see below) – with typically used doses for other indications for ivermectin, it is nearly impossible to hit the proposed IC50. While the Caly et al. in vitro model of apparent high potency against SARS-CoV-2 could be promising, this is in its extreme infancy well before there can be any consideration for clinical application. The dosing alone (among many other questions) would be completely unknown. Without appropriate dosing guidance, at the very least, it'll be impossible to know if the in vitro potency can be feasibility and safely replicated in humans.
    - 2.2 µM (lowest IC50) → 2.2 micromol/L → 0.0022 micromol/mL ------- FYI: M = mol/L
    - 875.1 g/mol (ivermectin molar mass) → 875.1 mcg/micromole
    - 0.0022 micromol/mL x 875.1 mcg/micromole = 19.25 mcg/mL = IC50
    - Ivermectin peak conc 0.24 mcg/ml (based on 12 mg dose → 0.08 mcg/mL PEAK – Sanford guide table 9A; assuming linear PK (to assume highest peak, best case scenario), 36 mg → peak of 0.24 mcg/mL)
        - If you factor in 93% protein binding – free drug PEAK is 0.017 mcg/mL
    - The roughly calculated dose required to reach the IC50 is well beyond what is known to be deemed safe

Appendix A: Remdesivir Clinical Trials for COVID-19

EMAIL: Pinki Bhatt, MD – RWJ-NB site PI (pb518@rwjms.rutgers.edu) and Fei Chen, RN – CRC research coordinator (chenf2@rwjms.rutgers.edu)

Please Note: All newly diagnosed COVID-19 positive patients will be reviewed daily by the study team to determine eligibility for enrollment into clinical trials.

Severe Study 5773 (Amd2)

Inclusion Criteria

1) Aged ≥ 18 years
2) SARS-CoV-2 infection ***confirmed*** by ***PCR test ≤ 4 days*** before randomization
3) Currently hospitalized
4) ***SpO_2 ≤ 94% on room air or requiring supplemental oxygen at screening***
5) Radiographic evidence of pulmonary infiltrates
6) Men and women of childbearing potential must agree to contraception

Exclusion Criteria

1) Participation in any other clinical trial of an experimental treatment for COVID-19
2) ***Concurrent treatment*** with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2 ***< 24 hours*** prior to study drug dosing ***(including azithromycin, hydroxychloroquine, tocilizumab)***
3) Evidence of ***multiorgan failure***
4) ***Mechanically ventilated (including V-V ECMO) ≥ 5 da***ys, or any duration of V-A ECMO
5) ***ALT or AST > 5 x ULN***
6) ***Creatinine clearance < 50*** mL/min using the Cockcroft-Gault formula
7) ***Positive pregnancy test***
8) Breastfeeding woman
9) Known hypersensitivity to the study drug, the metabolites, or formulation excipient

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Moderate Study 5774 (Amd1)

Inclusion Criteria

1) Aged ≥ 18 years (at all sites)
2) SARS-CoV-2 infection ***confirmed*** by ***PCR test ≤ 4 days*** before randomization
3) Currently hospitalized
4) **SpO2 > 94%** on room air at screening
5) Radiographic evidence of pulmonary infiltrates
6) Men and women of childbearing potential must agree to contraception

Exclusion Criteria

1) Participation in any other clinical trial of an experimental agent treatment for COVID-19
2) ***Concurrent treatment*** with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2 ***< 24 hours*** prior to study drug dosing ***(including azithromycin, hydroxychloroquine, tocilizumab)***
3) Requiring ***mechanical ventilation*** at screening
4) ***ALT or AST > 5 x ULN***
5) ***Creatinine clearance < 50*** mL/min using the Cockcroft-Gault formula
6) ***Positive pregnancy test***
7) Breastfeeding woman
8) Known hypersensitivity to the study drug, the metabolites, or formulation excipient

Appendix B: Rutgers Clinical Trial (CINJ 002011): HCQ alone vs. HCQ plus azithromycin for treatment of confirmed COVID-19

For enrollment evaluation, Mon-Fri, 730a-530p, **call**: 732-235-7356 or
email: statewide_research@cinj.rutgers.edu

Inclusion Criteria

1) Patients with proven SARS-CoV-2 infection by an accepted assay with symptoms consistent with COVID-19
2) Ability to measure and quantify viral load by quantitative PCR
3) Temperature >100.6 degrees F
4) Age 18 to 89 years
5) Ability to swallow oral medications
6) Patients must read, understand, and sign IRB approved informed consent

Exclusion Criteria

Subjects who meet any of the following exclusion criteria are not to be enrolled in this study:

1) Pregnancy or women who are breastfeeding
2) Two consecutive negative assays for SARS-CoV-2 infection
3) Patients that lack decision-making capacity will not be approached to participate in this study
4) Inability to tolerate oral medications
5) Allergy or prior adverse reaction to either azithromycin or hydroxychloroquine sulfate
6) QTc interval ≥450 mSEC
7) History of ongoing ventricular cardiac dysrhythmias of grade 2 as described by NCI CTCAE 5.0 criteria
8) History of serious ventricular arrhythmias (VT of VF > 3 beats in a row)

Drug	Dose	Special Notes	Drug Interactions	Warnings/ Adverse Drug Reactions	Monitoring
Hydroxychloroquine (HCQ)	PO: 400 mg BID x 1 day, then 400 mg once daily for at least 4 days Total: 5 days	**Compounded suspension available for NG/OG administration** *Safe in Pregnancy* *Dose adjustments not required*	QTc prolonging drugs May increase adverse/toxic effects of dapsone, specifically hemolytic reactions	**No current data regarding ADRs with HCQ use for COVID-19. The following are general precautions based on package insert and experience with chloroquine** • Extrapyramidal symptoms • Potential QTc prolongation • Corneal opacity • Aplastic anemia, thrombocytopenia, agranulocytosis or leukopenia	• CBC • BMP • Hepatic or renal dysfunction • EKG (QTc prolongation) • Routine testing for G6PD not required
Remdesivir (GS-5734)	IV: 200 mg x 1 day, then 100 mg daily for total 5 to 10 days	Acquired through expanded access program or clinical trial enrollment	Currently no drug-drug interactions observed at this point	First US Case: No adverse events observed	• CBC • BMP • Hepatic or renal dysfunction
Tocilizumab (Actemra®)	50-69 kg: give 400 mg IV 70-85 kg: give 600 mg IV >85 kg: 800 mg IV Maximum dose: 800 mg per dose	ID Consult Required **Reserved for critically ill**	May enhance immunosuppressive effects of other agents May decrease concentration of CYP3A substrates	• Neutropenia and thrombocytopenia • Hepatic injury and impairment • Risk of tuberculosis re-activation and new infection • CNS demyelination	• CBC • BMP • LFTs • TB Tests
Chloroquine	PO: 500 mg BID x 10 days	If ADRs occur, may reduce to 500 mg once daily Minimum course: 5 days **May be crushed**	In addition to those of HCQ: Antacids may decrease concentrations of chloroquine CYP 2D6 and CYP 3A4 metabolized drugs	See Hydroxychloroquine	• CBC • BMP • Hepatic or renal dysfunction • EKG (QTc prolongation)

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(almost all references are advance access online publication only at this time – Google the title to find published paper)

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